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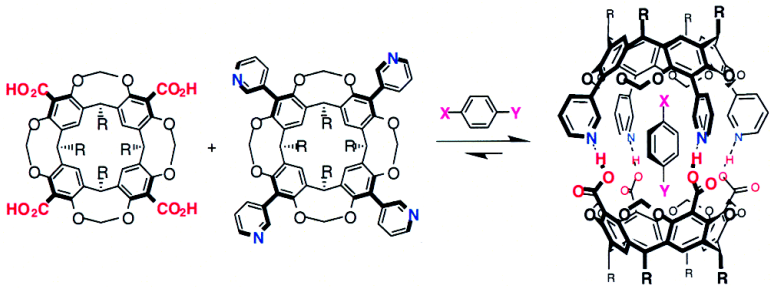

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Guest-Induced Assembly of Tetracarboxyl-Cavitand and Tetra(3-pyridyl)-Cavitand into a Heterodimeric Capsule via Hydrogen Bonds and CH−Halogen and/or CH−π Interaction: Control of the Orientation of the Encapsulated Guest

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Abstract: The guest- or solvent-induced assembly of a tetracarboxyl-cavitand **1** and a tetra(3-pyridyl)-cavitand **2** into a heterodimeric capsule **1·2** in a rim-to-rim fashion via four intermolecular $CO_2H\cdots N$ hydrogen bonds has been investigated both in solution and in the solid state. In the ^1H NMR study, a 1:1 mixture of **1a** and **2a** (R = $(CH_2)_6CH_3$) in $CDCl_3$ gave a mixture of various complicated aggregates, whereas this mixture in $CDCl_2CDCl_2$ or *p*-xylene-d_{10} exclusively produced the heterodimeric capsule **1a·2a**. It was found that an appropriate 1,4-disubstituted-benzene is a suitable guest for inducing the exclusive formation of **1a·2a** in $CDCl_3$. The ability of a guest to induce the formation of guest-encapsulating heterodimeric capsule, guest@(**1a·2a**), increased in the order *p*-ethyltoluene < 1-ethyl-4-methoxybenzene ≤ 1-ethyl-4-iodobenzene ≤ 1,4-dibromobenzene < 1-iodo-4-methoxybenzene ≤ 1,4-dimethoxybenzene ≤ 1,4-diiodobenzene. The ^1H NMR study revealed that a CH−halogen interaction between the inner protons of the methylene-bridge rims (-O-$H_{out}CH_{in}$-O-) of the **1a** and **2a** units and the halogen atoms of 1,4-dihalobenzenes and a CH−π interaction between the methoxy protons of 1,4-dimethoxybenzene and the aromatic cavities of the **1a** and **2a** units play important roles in the formation of 1,4-dihalobenzene@(**1a·2a**) and 1,4-dimethoxybenzene@-(**1a·2a**), respectively. A preliminary single-crystal X-ray diffraction analysis of guest@(**1b·2b**) (R = $(CH_2)_2$-Ph; guest = 1-iodo-4-methoxybenzene or *p*-xylene) confirmed that the guest encapsulated in **1b·2b** is oriented with the long axis of the guest along the long axis of **1b·2b** and that the iodo and the methoxy groups of the encapsulated 1-iodo-4-methoxybenzene are specifically oriented with respect to the cavities of the **2b** and **1b** units, respectively.

Introduction

Carcerands, in which two calix[4]resorcinarene cavitands are held together by four covalent linkages, have been synthesized and well-characterized by Cram and co-workers and have attracted considerable attention from the viewpoint of stabilization of reactive intermediates and microvesicles for drug delivery, by confinement of guest molecules inside the capsules from bulk phases.[1] Recently, supramolecular approaches based on noncovalent interactions through thermodynamic equilibration have proven to be a viable method for the formation of various types of molecular capsules.[2−9] The formation of heterodimeric capsules via hydrogen bonds (i.e., assembly of northern and southern hemispheres) is of considerable interest from the viewpoint of multicomponent assemblies and as the basis of a building block for molecular devices.[3,4,9] When compared with metal coordinations, hydrogen bonds have an advantage in the formation of heterodimeric capsules because two different but complementary functional groups in each hemisphere would be directly associated with each other. A hydrogen bond between carboxylic acid and pyridyl groups is a reliable supramolecular synthon for heterotopic dimerization.[4,9a,9b,10] Guest-induced capsule formation via dynamic assembly is

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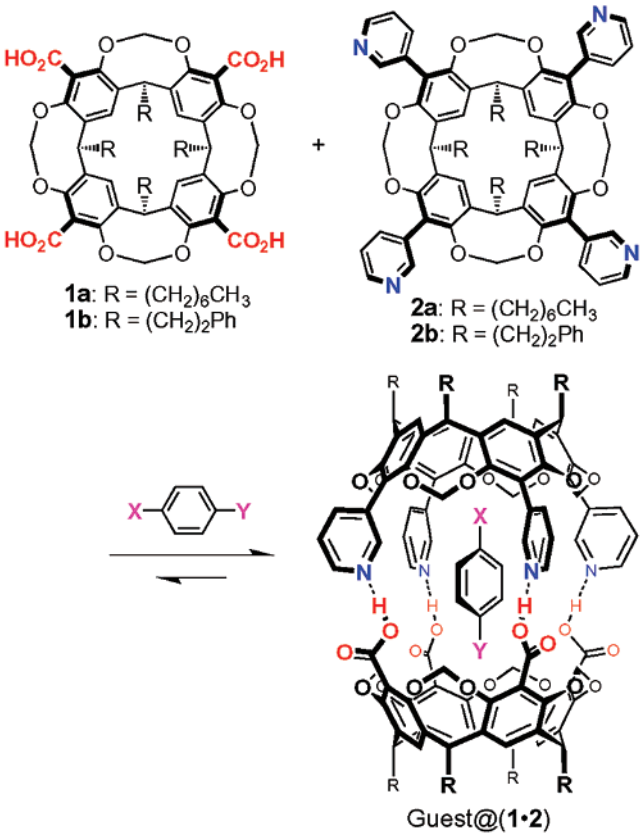
another interesting topic, with a view to mimicking biological processes, as well as a dynamic combinatorial library of assemblies.[2f,3,11] Upon addition of an appropriate guest, a mixture of various aggregates formed by reversible association in a thermodynamic equilibration would be shifted most favorably toward formation of a capsule by the guest-induced or -templated stabilization through noncovalent interactions, in which a guest@capsule becomes the most favored aggregate.[11] Here, we report the guest-induced exclusive formation of a hydrogen-bonded heterodimeric capsule **1·2** assembled by a tetracarboxyl-cavitand **1** and a tetra(3-pyridyl)-cavitand **2**, in which one molecule of an appropriate 1,4-disubstituted-benzene guest such as 1,4-diiodobenzene, 1,4-dimethoxybenzene, or 1-iodo-4-methoxybenzene is encapsulated in **1·2** (Scheme 1). Capsule−guest CH−halogen and/or guest−capsule CH−π interactions play an essential role in the formation of guest@(**1·2**), cooperatively, with the complementary $CO_2H\cdots N$ hydrogen bonds between **1** and **2** and in the strict control of the orientation of an encapsulated guest.

Scheme 1



Experimental Procedures

General. THF was distilled from sodium-benzophenone ketyl under an argon atmosphere. The other solvents and all commercially available reagents were used without any purification. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC300 spectrometer. FAB-MS spectra were measured on a JEOL JMS-SX102a spectrometer. ESI- and CSI-MS spectra were obtained on a JEOL JMS-700 spectrometer. IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Halogenated and aromatic NMR solvents were dried over anhydrous potassium carbonate and molecular sieves 4A, respectively, prior to use. The tetracarboxyl-cavitands **1** were prepared according to the literature.[2d,12a]

Tetra(3-pyridyl)-Cavitand (2a) (R = $(CH_2)_6CH_3$). To a solution of tetrabromocavitand (4.357 g, 3.50 mmol) in dry THF (180 mL) at −78 °C under an argon atmosphere was added a hexane solution of *n*-BuLi (1.53 M, 11.4 mL, 17.4 mmol) over a period of 1 min. After stirring for 30 min, to the resulting solution was added $B(OMe)_3$ (7.0 mL, 62.4 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 2 h, warmed to room temperature over a period of 5 h, and then quenched with 1 M HCl (20 mL). After evaporation of solvents, the residue was partitioned between Et_2O (300 mL) and water (100 mL), and the organic layer was washed with water (100 mL × 3). After evaporation of solvents, the pale yellow solid residue was used as a cavitand tetraboronic acid to the next reaction without further purification.

To the crude cavitand tetraboronic acid and $Pd(PPh_3)_4$ (809 mg, 0.700 mmol) under an argon atmosphere were successively added argon-saturated toluene (60 mL), argon-saturated EtOH (40 mL), argon-saturated aqueous Na_2CO_3 (2 M, 10 mL), and 3-bromopyridine (4.0 mL, 41.5 mmol). The resulting mixture was stirred at refluxing temperature for 72 h. After cooling to room temperature and evaporation of solvents, the residue was partitioned between $CHCl_3$ (300 mL) and water (100 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried over Na_2SO_4. After evaporation of solvents, the residue was subjected to column chromatography on Al_2O_3 eluted with $CHCl_3$ and then EtOAc-EtOH (1:1) to give slightly crude **2a**, which was dissolved in $CHCl_3$ (15 mL) and poured into MeOH (100 mL) to give pure **2a** as a white solid (998 mg, 23% yield). Mp 167−169 °C; ^{1}H NMR ($CDCl_3$, 23 °C) δ 0.92 (t, J = 6.9 Hz, 12H), 1.22−1.65 (m, 40H), 2.30−2.42 (m, 8H), 4.26 (d, J = 7.0 Hz, 4H), 4.86 (t, J = 7.9 Hz, 4H), 5.29 (d, J = 7.0 Hz, 4H), 7.26 (dd, J = 4.6 and 7.8 Hz, 4H), 7.38 (s, 4H), 7.42 (d, J = 7.8 Hz, 4H), 8.26 (d, J = 1.5 Hz, 4H), 8.49 (dd, J = 1.5 and 4.6 Hz, 4H); IR (KBr) ν 2927, 1464, 1408, 1267, 1086, 964 cm^{-1}; FAB-MS (NBA) *m*/*z* 1238 ([**2a** + H]$^+$). Anal. Calcd for $C_{80}H_{92}N_4O_8$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.38; H, 7.80; N, 4.32.

Tetra(3-pyridyl)-Cavitand (2b) (R = $(CH_2)_2Ph$). According to the same reaction and workup conditions for the preparation of **2a**, the cavitand **2b** was obtained as a white solid in 20% yield. Mp >300 °C; ^{1}H NMR ($CDCl_3$, 23 °C) δ 2.62−2.80 (m, 16H), 4.27 (d, J = 6.9 Hz,

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4H), 4.97 (t, J = 7.6 Hz, 4H), 5.30 (d, J = 6.9 Hz, 4H), 7.18−7.33 (m, 24H), 7.42 (s, 4H), 7.44 (d, J = 7.9 Hz, 4H), 8.27 (d, J = 1.3 Hz, 4H), 8.49 (dd, J = 1.3 and 4.6 Hz, 4H); FAB-MS (NBA) m/z 1262 ([**2b** + H]$^+$). Anal. Calcd for $C_{84}H_{68}N_4O_8$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.82; H, 5.68; N, 4.25.

Heterodimeric Capsule 1a·2a. Mp 235−237 °C (dec); ^{1}H NMR ($CDCl_2CDCl_2$, 23 °C) δ 0.87 (t, J = 7.0 Hz, 24H), 1.16−1.99 (m, 80H), 2.08−2.48 (m, 16H), 3.88 (brs, 4H), 4.47 (d, J = 7.3 Hz, 4H), 4.73 (t, J = 8.0 Hz, 4H), 4.77 (t, J = 8.0 Hz, 4H), 5.27 (brs, 4H), 5.69 (d, J = 7.3 Hz, 4H), 7.15 (s, 4H), 7.38 (s, 4H), 7.53 (dd, J = 4.9 and 7.7 Hz, 4H), 7.72 (d, J = 7.7 Hz, 4H), 7.85 (brs, 4H), 8.83 (d, J = 4.9 Hz, 4H); ^{1}H NMR (*p*-xylene-d_{10}, 23 °C) δ 0.93 (t, J = 7.0 Hz, 12H), 0.94 (t, J = 7.0 Hz, 12H), 1.11−1.67 (m, 80H), 2.10−2.61 (m, 16H), 4.28 (d, J = 7.0 Hz, 4H), 4.96−5.18 (m, 16H), 5.83 (d, J = 7.1 Hz, 4H), 6.73 (dd, J = 5.0 and 7.8 Hz, 4H), 7.12 (d, J = 7.8 Hz, 4H), 7.43 (s, 4H), 7.68 (s, 4H), 7.79 (s, 4H), 9.02 (d, J = 5.0 Hz, 4H); IR (KBr) ν 2927, 2472, 1923, 1730, 1456, 1288, 1088, 968 cm^{-1}; Negative-mode ESI-MS (*p*-xylene as a solvent and Ph_4PCl as a charge carrier; ion source temperature = 230 °C) m/z (%) 2342 (4, [**1a·2a**]$^-$), 1272 (100, [**2a** + Cl]$^-$), 1104 (65, [**1a** − H]$^-$).

1,4-Diiodobenzene@(1a·2a). ^{1}H NMR ($CDCl_3$, 23 °C) δ 0.92 (t, J = 6.9 Hz, 12H), 0.93 (t, J = 6.7 Hz, 12H), 1.20−1.71 (m, 80H), 2.18−2.49 (m, 16H), 4.39 (d, J = 6.8 Hz, 4H), 4.86 (t, J = 8.0 Hz, 8H), 4.91 (d, J = 7.1 Hz, 4H), 5.20 (d, J = 6.8 Hz, 4H), 5.67 (d, J = 7.1 Hz, 4H), 6.47 (d, J = 8.3 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 7.17 (s, 4H), 7.38 (s, 4H), 7.50 (d, J = 1.5 Hz, 4H), 7.54 (dd, J = 5.1 and 8.0 Hz, 4H), 7.73 (dt, J = 1.5 and 8.0 Hz, 4H), 8.96 (dd, J = 1.5 and 5.1 Hz, 4H); Negative-mode CSI-MS ($CHCl_3$ as a solvent and Ph_4PCl as a charge carrier; ion source temperature = 0 °C) m/z (%) 2707.32 (calcd. 2708.05) (52, [1,4-diiodobenzene@(**1a·2a**) + Cl]$^-$), 2377.73 (calcd. 2378.21) (100, [**1a·2a** + Cl]$^-$).

1,4-Dimethoxybenzene@(1a·2a). ^{1}H NMR ($CDCl_3$, 23 °C) δ 0.23 (s, 3H), 0.36 (s, 3H), 0.92 (t, J = 6.9 Hz, 12H), 0.93 (t, J = 6.7 Hz, 12H), 1.20−1.71 (m, 80H), 2.18−2.49 (m, 16H), 4.11 (d, J = 7.0 Hz, 4H), 4.68 (d, J = 7.4 Hz, 4H), 4.88 (t, J = 8.0 Hz, 8H), 5.21 (d, J = 7.0 Hz, 4H), 5.70 (d, J = 7.4 Hz, 4H), 5.95 (d, J = 9.0 Hz, 2H), 6.29 (d, J = 9.0 Hz, 2H), 7.23 (s, 4H), 7.44 (s, 4H), 7.52 (dd, J = 5.0 and 7.9 Hz, 4H), 7.63 (d, J = 1.5 Hz, 4H), 7.68 (dt, J = 1.5 and 7.9 Hz, 4H), 8.96 (dd, J = 1.5 and 5.0 Hz, 4H); Negative-mode CSI-MS ($CHCl_3$ as a solvent and Ph_4PCl as a charge carrier; ion source temperature = 0 °C) m/z (%) 2753.0 (calcd. 2752.3) (55, [**1a·2a** + Ph_4PCl + Cl]$^-$), 2516.6 (calcd. 2516.2) (61, [1,4-dimethoxybenzene@(**1a·2a**) + Cl]$^-$), 2377.2 (calcd. 2378.2) (100, [**1a·2a** + Cl]$^-$).

1-Iodo-4-methoxybenzene@(1a·2a). ^{1}H NMR ($CDCl_3$, 23 °C) δ 0.36 (s, 3H), 0.92 (t, J = 6.9 Hz, 12H), 0.93 (t, J = 6.7 Hz, 12H), 1.20−1.71 (m, 80H), 2.18−2.49 (m, 16H), 4.47 (d, J = 6.8 Hz, 4H), 4.64 (d, J = 7.3 Hz, 4H), 4.86 (t, J = 8.0 Hz, 4H), 4.87 (t, J = 8.0 Hz, 4H), 5.18 (d, J = 6.8 Hz, 4H), 5.71 (d, J = 7.3 Hz, 4H), 6.17 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 7.24 (s, 4H), 7.39 (s, 4H), 7.53 (dd, J = 5.0 and 7.9 Hz, 4H), 7.57 (d, J = 1.5 Hz, 4H), 7.74 (dt, J = 1.5 and 7.9 Hz, 4H), 8.96 (dd, J = 1.5 and 5.0 Hz, 4H); Negative-mode CSI-MS ($CHCl_3$ as a solvent and Ph_4PCl as a charge carrier; ion source temperature = 0 °C) m/z (%) 3126.9 (calcd. 3127.4) (15, [**1a·2a** + 2Ph_4PCl + Cl]$^-$), 2752.5 (calcd. 2752.3) (46, **1a·2a** + Ph_4PCl + Cl]$^-$), 2611.3 (calcd. 2612.2) (60, [1-iodo-4-methoxybenzene@(**1a·2a**) + Cl]$^-$), 2377.9 (calcd. 2378.2) (100, [**1a·2a** + Cl]$^-$).

X-ray Data Collection and Crystal Structure Determinations. X-ray diffraction data were collected on a Bruker CCD/Smart 1000 diffractometer with graphite monochromated MoKα radiation. The structures were solved by direct methods (SIR 92 or SIR97)[31] and refined with a full-matrix least-squares procedure using the program teXsan.[32] All non-hydrogen atoms were refined with anisotropic displacement parameters. The measurement conditions and structural details are listed in Table 3 (and see Supporting Information).

Results and Discussion

Synthesis and Solubility of Cavitands 1 and 2. The tetracarboxyl-cavitands **1** (**a**: R = $(CH_2)_6CH_3$, **b**: R = $(CH_2)_2$-Ph) were prepared by the lithiation of tetrabromocavitands with *n*-BuLi, followed by carbonation with CO_2 gas.[2d,12a] The tetra-(3-pyridyl)-cavitands **2** (**a**: R = $(CH_2)_6CH_3$, **b**: R = $(CH_2)_2$-

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(23) The assignment of signals of guest@(**1a·2a**) was carried out by the NOE experiment and the H−H COSY spectroscopy.
(24) The calculated molecular volumes of 1,4-disubstituted-benzene guests (Å^3) are as follows:[16] 1,4-dichlorobenzene, 114.59; 1,4-dibromobenzene, 129.28; 1,4-diiodobenzene, 144.01; 1,4-dimethoxybenzene, 135.13; 1-iodo-4-methoxybenzene, 139.54; 1-ethyl-4-iodobenzene, 148.31; 1-ethyl-4-methoxybenzene, 143.81; *p*-ethyltoluene, 136.03; 1,4-diethylbenzene, 153.16; and 1,4-bis(trifluoromethyl)benzene, 135.05.
(25) The NOE experiments were carried out in a 1:1:1 mixture of **1a**, **2a**, and a guest (16.0 mM each) in $CDCl_3$ at 23 °C. The mixing times of 3.0 and 2.4 s were used for 1,4-diiodobenzene@(**1a·2a**) and 1,4-dimethoxybenzene@-(**1a·2a**), respectively. The NOEs on **2a** alone in $CDCl_3$ were scarcely observed at C2- and C4-hydrogens of the 3-pyridyl group upon irradiation of the inner hydrogen of the methylene-bridge rim, suggesting conformational rotation of the 3-pyridyl group.
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(27) CSI-MS is a method for the low-temperature measurement of ESI-MS, wherein the ion source temperature is the range from −20 °C to room temperature. The CSI-MS is a very powerful method for the detection of supramolecular aggregates, and the molecular mass observed fairly reflects the structure in solution. (a) Sakamoto, S.; Fujita, M.; Kim, K.; Yamaguchi, K. *Tetrahedron* **2000**, *56*, 955−964. (b) Sakamoto, S.; Yamaguchi, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 905−908 and references therein.
(28) The structural parameters for 1-iodo-4-methoxybenzene@(**1b·2b**) and *p*-xylene@(**1b·2b**) reported here are still preliminary. Even from the data collected at low temperature, we have not yet obtained satisfactory parameters because of the severe disorder and cannot precisely discuss bond lengths, bond angles, and interatomic distances. For example, the O···N distances of the four intermolecular CO_2H···N hydrogen bonds are 2.28, 2.31, 2.42, and 2.54 Å for 1-iodo-4-methoxybenzene@(**1b·2b**) and 2.24, 2.39, 2.44, and 2.45 Å for *p*-xylene@(**1b·2b**). Although the final level has not yet been reached, we think the data obtained here are significant enough to demonstrate the supramolecular structure of guest@(**1b·2b**).
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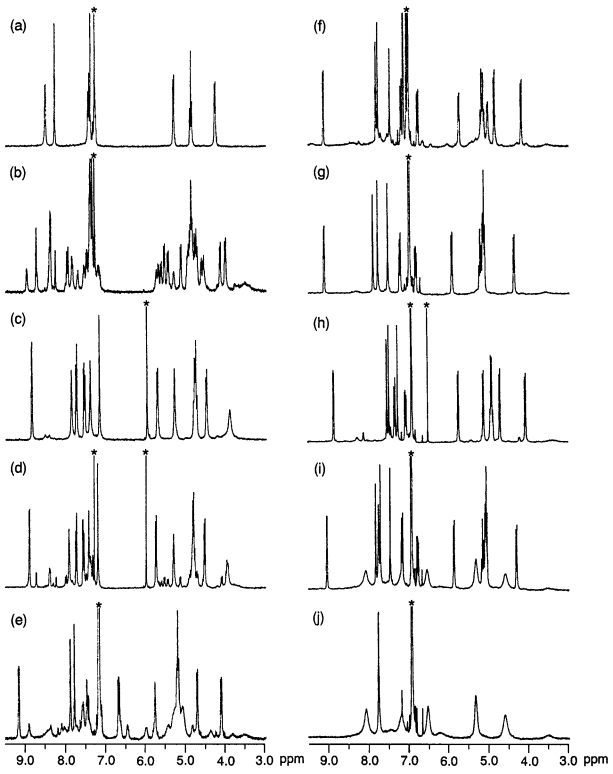

Figure 1. ^{1}H NMR spectra at 23 °C: (a) **2a** alone (4.0 mM) in $CDCl_3$; a 1:1 mixture of **1a** and **2a** (4.0 mM each) in (b) $CDCl_3$, (c) $CDCl_2CDCl_2$, (d) a 1:1 mixture of $CDCl_3$ and $CDCl_2CDCl_2$, (e) benzene-d_6, (f) toluene-d_8, (g) *p*-xylene-d_{10}, and (h) a 1:1 mixture of $CDCl_3$ and *p*-xylene-d_{10}; (i) a 1:2 mixture of **1a** and **2a** ([**2a**] = 8.0 mM) in *p*-xylene-d_{10}; and (j) **2a** alone (4.0 mM) in *p*-xylene-d_{10}. The residual solvent signals are marked with an asterisk.

Ph) were prepared by the Pd-catalyzed Suzuki cross-coupling reaction of cavitand tetraboronic acids with 3-bromopyridine.[12b] Recently, Reinhoudt and co-workers reported the synthesis of a tetracarboxyl-cavitand and a tetra(3-pyridyl)-cavitand, in which the hydrogen bonding sites are connected to the cavitand core by alkoxy linkers, and their assembly into a hydrogen-bonded heterodimeric capsule in $CDCl_3$.[4] In our system, the carboxyl group in **1** and the 3-pyridyl group in **2** are directly connected to the cavitand core so as to minimize free rotation between the hydrogen bonding sites and the cavitand core and to make the electronic nature of the hydrogen bonding groups influence that of the cavitand core.

The tetracarboxyl-cavitand **1a** is sparingly soluble in $CHCl_3$ at room temperature and completely insoluble in benzene, toluene, *p*-xylene, and mesitylene, owing to a hydrogen-bonded self-aggregation,[2d,13] whereas the tetra(3-pyridyl)-cavitand **2a** is soluble in these solvents. A solubility test of **1a** indicated that addition of 1 equiv of **2a** to **1a** is essential for the complete dissolution of **1a** in these solvents. The solubility of a 1:1 mixture of **1a** and **2a** in *p*-xylene is more than 30 mM.

Solvent Effect of Heterodimeric Capsule 1·2. The ^{1}H NMR spectra of **2a** alone and a 1:1 mixture of **1a** and **2a** showed unique behavior. In the case of **2a** alone, the ^{1}H NMR spectrum in $CDCl_3$ showed sharp signals (Figure 1a), whereas the spectrum in *p*-xylene-d_{10} exhibited broad signals (Figure 1j). In the case of a 1:1 mixture of **1a** and **2a**, the ^{1}H NMR spectrum in $CDCl_3$ or CD_2Cl_2 showed complicated signals indicating various species of aggregates (Figure 1b), whereas only a single species composed of **1a** and **2a** in a 1:1 ratio was quantitatively

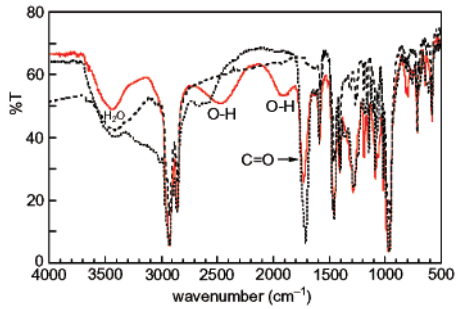

Figure 2. IR spectra (KBr) of (a) **1a** (dotted line), (b) **2a** (dashed line), and (c) **1a·2a** (red line).

produced in $CDCl_2CDCl_2$ or *p*-xylene-d_{10} (Figure 1c,g). The formation of a single species was qualitatively more favorable in *p*-xylene-d_{10} than in $CDCl_2CDCl_2$ (Figure 1d vs 1h). As shown in Figure 1b−h, the quantity of the single species arising from the 1:1 composition of **1a** and **2a** increased in the order CD_2Cl_2, $CDCl_3 \ll$ benzene-d_6 < toluene-d_8 < $CDCl_2CDCl_2 \leq$ *p*-xylene-d_{10}. However, the ^{1}H NMR spectrum in mesitylene-d_{12} again showed complicated signals.

A 2:1 mixture of **1a** and **2a** in *p*-xylene-d_{10} gave a ^{1}H NMR spectrum identical to that of a 1:1 mixture of **1a** and **2a**, although half of the **1a** remained insoluble. In contrast, the ^{1}H NMR spectrum of a 1:2 mixture of **1a** and **2a** in *p*-xylene-d_{10} exhibited free **2a** in addition to the single species composed of the 1:1 ratio of **1a** and **2a** (Figure 1i). The NOE experiment on a 1:1 mixture of **1a** and **2a** in *p*-xylene-d_{10} showed −2.7 and 0% NOEs at the C2- and C4-hydrogens of the 3-pyridyl group, respectively, upon irradiation of the inner hydrogen of the methylene-bridge rim (O-$H_{out}CH_{in}$-O) of the **2a** unit. This suggests that the C2-hydrogen, i.e., the N atom of the 3-pyridyl group is directed inward to the cavity of the **2a** unit. This orientation is required for heterodimeric capsule formation. These results indicate that each molecule of **1a** and **2a** assembles into a heterodimeric capsule **1a·2a** in *p*-xylene-d_{10} or $CDCl_2$-$CDCl_2$ through four intermolecular $CO_2H\cdots N$ hydrogen bonds (Scheme 1).[14] The CPK model of **1a·2a** indicates that *p*-xylene is the most suitable guest among the solvents investigated here for fitting well within the capsule. Ineffective capsule self-assembly of **1a·2a** in $CDCl_3$ could be explained by the concept of 55% solution proposed by Rebek and Mecozzi.[15,16] The encapsulation of *p*-xylene in **1a·2a** was confirmed by X-ray crystallographic analysis (vide infra). The heterodimeric capsule **1a·2a** in *p*-xylene-d_{10} or $CDCl_2CDCl_2$ is stable at least at concentrations greater than 0.1 mM but is disrupted upon the addition of DMSO-d_6 as a cosolvent.

In the IR spectrum of **1a·2a** (KBr), the broad O−H stretching bands of the CO_2H group appeared at very low wavenumbers, namely, ν 2472 and 1923 cm^{-1}, which are characteristic of a carboxylic acid hydrogen bonded to a pyridyl nitrogen (Figure 2).[9b,17] Furthermore, the carbonyl stretching band appeared at ν 1730 cm^{-1}, suggesting that no proton transfer had occurred. The negative-mode ESI-MS spectrum of a 1:1 mixture of **1a** and **2a** in *p*-xylene, in the presence of Ph_4PCl as a charge carrier, indicated a heterodimeric capsule **1a·2a**, in which a molecular ion peak was observed at *m*/*z* 2342 $[\mathbf{1a\cdot 2a}]^-$ (Figure 3a).[18]

Guest-Induced Assembly of Heterodimeric Capsule 1·2 in $CDCl_3$. The cavitand possesses a bowl-shaped cavity composed of four electron-rich resorcinol rings and a rim composed of four polarized methylene bridges (-O-CH_2-O-). It

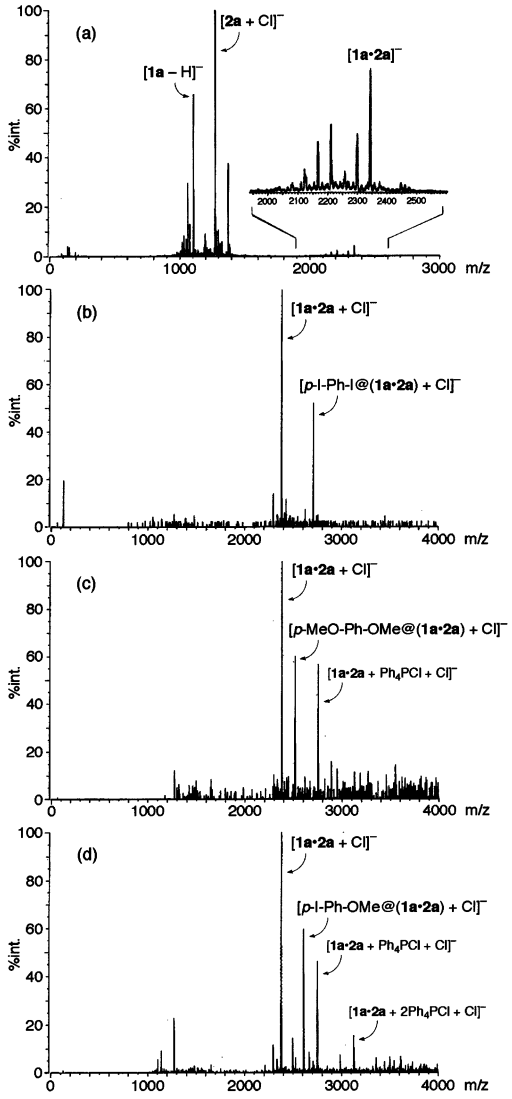

Figure 3. (a) Negative-mode ESI-MS spectrum of **1a·2a** (*p*-xylene as a solvent and Ph_4PCl as a charge carrier; ion source temperature = 230 °C). Negative-mode CSI-MS spectra of (b) 1,4-diiodobenzene@(**1a·2a**), (c) 1,4-dimethoxybenzene@(**1a·2a**), and (d) 1-iodo-4-methoxybenzene@(**1a·2a**) ([**1a**] = [**2a**] = [guest] = 4.0 mM and [Ph_4PCl] = 1.3 mM in $CHCl_3$; ion source temperature = 0 °C).

is expected that calix[4]resorcinarene and its cavitand can accommodate a guest in the cavity via a CH−π interaction[13,19,20] or halogen−π interaction[21] with the electron-rich resorcinol rings or CH−halogen interaction[22] with the methylene-bridge rim. We found that 1,4-dibromobenzene, 1,4-diiodobenzene, 1,4-dimethoxybenzene, 1-iodo-4-methoxybenzene, 1-ethyl-4-iodobenzene, and 1-ethyl-4-methoxybenzene are suitable guests for inducing the exclusive formation of the heterodimeric capsule **1a·2a** in $CDCl_3$. The addition of these guests to a mixture of various complicated aggregates of **1a** and **2a** shifted the thermodynamic equilibrium of the mixture toward the guest-encapsulating heterodimeric capsule, guest@(**1a·2a**). The representative ^{1}H NMR spectra of a 1:1 mixture of **1a** and **2a** (4.0 mM each) in the presence of guests in $CDCl_3$ at 23 °C are shown in Figure 4.[23,24] The representative chemical shifts of guest@(**1a·2a**) and their chemical shift changes ($\Delta\delta$) relative to free guests and free **2a** are summarized in Table 1. The following features (items 1−6) are noteworthy with regards to the formation of guest@(**1a·2a**) in $CDCl_3$.

Item 1: Association behavior of guest@(**1a·2a**). The signals of free and encapsulated guests appeared independently because the exchange of guests in and out of the heterodimeric capsule **1a·2a** is slow on the NMR time scale. The signals of encapsulated guests were shifted upfield relative to those of free guests, owing to the ring current effect of the aromatic cavities of **1a·2a**. Furthermore, in marked contrast to free guests, in which the aromatic protons appear as one singlet peak for 1,4-dibromobenzene, 1,4-diiodobenzene, and 1,4-dimethoxybenzene, the aromatic protons of these guests encapsulated in **1a·2a** appeared as two doublet peaks ($\Delta\delta = -0.70 \sim -0.95$ and $-0.32 \sim -0.38$) as shown in Figure 4a−c. The methoxy protons of the encapsulated 1,4-dimethoxybenzene also appeared as two singlet peaks ($\Delta\delta = -3.42$ and -3.55). As the electronic environment of the **1a** as a southern hemisphere is different from that of **2a** as a northern hemisphere, the inherently symmetrical guests become nonsymmetrical when encapsulated in **1a·2a**. The corresponding results in the ^{1}H NMR spectra are characteristic of species encapsulated in a heterodimeric capsule. The integration ratio of these signals in the ^{1}H NMR spectra established the 1:1 stoichiometry of the heterodimeric capsule (**1a·2a**)−guest assembly. In the ^{1}H NMR spectrum of a mixture of **1a** (4.0 mM), **2a**, and 1,4-diiodobenzene in a 1:2:2 ratio, a mixture of 1,4-diiodobenzene@(**1a·2a**), free **2a**, and free 1,4-diiodobenzene was observed in a 1:1:1 ratio, indicating that the exchange of the **2a** unit in the heterodimeric capsule and free **2a** is also slow on the NMR time scale.

Item 2: Orientation of encapsulated symmetrical guest. The NOE experiment on 1,4-diiodobenzene@(**1a·2a**) showed 4.7 and 2.0% NOEs at the large and small upfield shifted aromatic hydrogens (δ 6.47 and 7.04) of the encapsulated guest, respectively, and −7.3 and 0% NOEs at the C2- and C4-hydrogens of the 3-pyridyl group, respectively, upon irradiation of the inner hydrogen of the methylene-bridge rim (-O-H_{out}-CH_{in}-O-) of the **2a** unit (Figure 5).[25] The NOE experiment on 1,4-dimethoxybenzene@(**1a·2a**) gave a similar result.[25] These results indicate that (1) 1,4-disubstituted-benzene encapsulated in **1a·2a** is oriented with the long axis of the guest along the long axis of **1a·2a**, (2) the guest does not tumble within **1a·2a** on the NMR time scale,[2c] and (3) the larger upfield shifted aromatic proton of the encapsulated guest is oriented toward the **2a** unit (Figure 5a,b). The results also indicate that the C2-hydrogen, i.e., the N atom of the 3-pyridyl group of the **2a** unit is directed inward to the capsule,[25] the orientation of which is essential for the formation of heterodimeric capsule. In all cases, the C2- and C6-protons of the 3-pyridyl group in guest@(**1a·2a**) were shifted upfield by 0.63∼0.76 ppm and downfield by 0.45∼0.47 ppm, respectively, as compared with those of **2a** alone. This result also supports the finding that the C2-proton of the 3-pyridyl group in guest@(**1a·2a**) is directed inward to the capsule, wherein the upfield shift of the C2-proton would result from the ring current effect of the aromatic cavity of **1a·2a** and/or the encapsulated guest.

Item 3: CH−halogen interaction. The 1,4-diiodobenzene@(**1a·2a**) was formed by the addition of at least 2 equiv of 1,4-diiodobenzene to a 1:1 mixture of **1a** and **2a** (4.0 mM each) (Figure 4b). On the other hand, to achieve the formation of 1,4-dibromobenzene@(**1a·2a**), at least 30 equiv of 1,4-dibromobenzene was required (Figure 4a). In marked contrast, there was no formation of guest@(**1a·2a**) even when more than 30 equiv

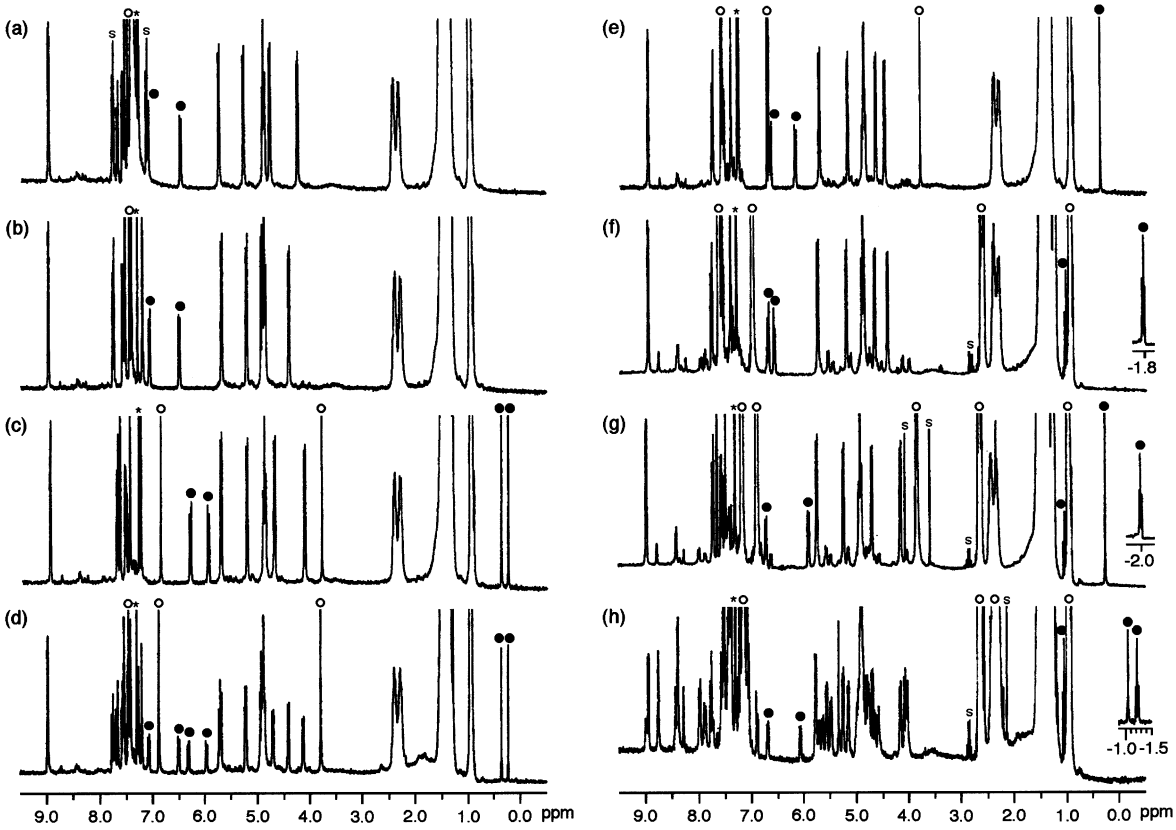

Figure 4. ^{1}H NMR spectra of a 1:1 mixture of **1a** and **2a** (4.0 mM each) in $CDCl_3$ at 23 °C in the presence of (a) 30 equiv of 1,4-dibromobenzene, (b) 2 equiv of 1,4-diiodobenzene, (c) 2 equiv of 1,4-dimethoxybenzene, (d) a 1:1 mixture of 1,4-diiodobenzene and 1,4-dimethoxybenzene (2 equiv each), (e) 2 equiv of 1-iodo-4-methoxybenzene, (f) 30 equiv of 1-ethyl-4-iodobenzene, (g) 30 equiv of 1-ethyl-4-methoxybenzene, and (h) 30 equiv of *p*-ethyltoluene. The signals of the encapsulated and free guests, the spinning sidebands of excess free guest, and the residual solvent are marked with a solid circle, open circle, s, and an asterisk, respectively.

Table 1. Representative Chemical Shifts (δ) of 1,4-Disubstituted-Benzene@(**1a·2a**) in $CDCl_3$ and their Chemical Shift Changes ($\Delta\delta$) Relative to Free Guests and Free **2a**[a]

	p-Br-Ph-Br @(**1a·2a**)	*p*-I-Ph-I @(**1a·2a**)	*p*-MeO-Ph-OMe @(**1a·2a**)	*p*-MeO-Ph-I @(**1a·2a**)	*p*-Et-Ph-I @(**1a·2a**)	*p*-MeO-Ph-Et @(**1a·2a**)	*p*-Et-Ph-Me @(**1a·2a**)
Ar-H of guest	6.43, 7.05	6.47, 7.04	5.95, 6.29	6.17,[b] 6.64[c]	6.55,[d] 6.67[e]	5.87,[f] 6.68[g]	6.04, 6.65
$\Delta\delta$	−0.94, −0.32	−0.95, −0.38	−0.70, −0.36	−0.52,[b] −0.93[c]	−0.30,[d] −0.93[e]	−0.98,[f] −0.45[g]	−1.08, −0.47[h]
CH_3O of guest			0.23, 0.36	0.36		0.25	−1.06[i]
$\Delta\delta$			−3.55, −3.42	−3.43		−3.55	−3.41
CH_3CH_2 of guest[j]					−1.78	−1.99	−1.23
$\Delta\delta$					−3.00	−3.21	−2.48
O-HCH_{inner}-O of **1a**	4.73	4.91	4.68	4.64	4.65	4.67	4.67
$\Delta\delta$[k]	0.05	0.23		−0.04	−0.03	−0.01	−0.01
O-HCH_{outer}-O of **1a**	5.70	5.67	5.70	5.71	5.73	5.71	5.74
$\Delta\delta$[k]	0.00	−0.03		0.01	0.03	0.01	0.04
O-HCH_{inner}-O of **2a**	4.21	4.39	4.11	4.47	4.41	4.13	4.06
$\Delta\delta$	−0.05	0.13	−0.15	0.21	0.15	−0.13	−0.20
$\Delta\delta$[k]	0.10	0.28		0.36	0.30	0.02	−0.05
O-HCH_{outer}-O of **2a**	5.23	5.20	5.21	5.18	5.19	5.21	5.23
$\Delta\delta$	−0.06	−0.09	−0.08	−0.11	−0.10	−0.08	−0.06
$\Delta\delta$[k]	0.02	−0.01		−0.03	−0.02	0.00	0.02
Py-C2-H of **2a**	7.50	7.50	7.63	7.57	7.54	7.61	7.51
$\Delta\delta$	−0.76	−0.76	−0.63	−0.69	−0.72	−0.65	−0.75
Py-C6-H of **2a**	8.96	8.96	8.96	8.96	8.95	8.95	8.94
$\Delta\delta$	0.47	0.47	0.47	0.47	0.46	0.46	0.45
Ar-H of **1a**	7.23	7.17	7.23	7.24	7.27	7.27	—[l]
Ar-H of **2a**	7.44	7.38	7.44	7.39	7.38	7.45	—[l]

[a] [**1a**] = [**2a**] = 4.0 mM and [guest] = 8.0 mM in $CDCl_3$ at 23 °C for 1,4-diiodobenzene, 1,4-dimethoxybenzene, and 1-iodo-4-methoxybenzene. [**1a**] = [**2a**] = 4.0 mM and [guest] = 120 mM in $CDCl_3$ at 23 °C for 1,4-dibromobenzene, 1-ethyl-4-iodobenzene, 1-ethyl-4-methoxybenzene, and *p*-ethyltoluene. $\Delta\delta = \delta$(guest@(**1a·2a**)) − δ(free guest or free **2a**). [b] *o*-Ar-H with respect to the methoxy group. [c] *o*-Ar-H with respect to the iodo group. [d] *o*-Ar-H with respect to the ethyl group. [e] *o*-Ar-H with respect to the iodo group. [f] *o*-Ar-H with respect to the methoxy group. [g] *o*-Ar-H with respect to the ethyl group. [h] *o*-Ar-Hs with respect to the methyl and ethyl groups cannot be assigned. [i] Methyl group. [j] The signal of methylene in the ethyl group of encapsulated guest is overlapped with the signals of methyl groups of host or free guest. [k] δ(guest@(**1a·2a**)) − δ(1,4-dimethoxybenzene@(**1a·2a**)). [l] The signal cannot be assigned.

of 1,4-dichlorobenzene, 1,3-diiodobenzene, or iodobenzene was added. The shape and size of a guest with respect to the cavity of **1a·2a** are undoubtedly important factors.[15,24] The signals of the inner protons of the methylene-bridge rims of the **1a** and

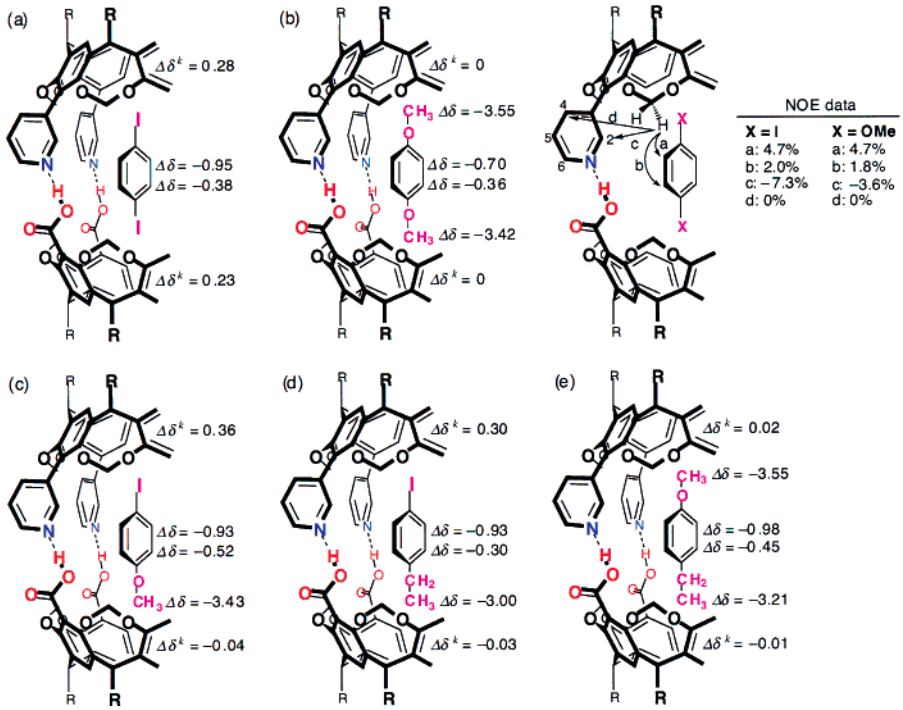

Figure 5. Schematic representation of (a) 1,4-diiodobenzene@(**1a·2a**), (b) 1,4-dimethoxybenzene@(**1a·2a**), (c) 1-iodo-4-methoxybenzene@(**1a·2a**), (d) 1-ethyl-4-iodobenzene@(**1a·2a**), and (e) 1-ethyl-4-methoxybenzene@(**1a·2a**). The NOE data are shown in panels a and b, and the chemical shift changes of the encapsulated guest relative to free guest ($\Delta\delta$) and of the inner protons of methylene-bridge rims of guest@(**1a·2a**) relative to those of 1,4-dimethoxybenzene@(**1a·2a**) ($\Delta\delta^k$) are shown in all cases.

2a units in 1,4-dihalobenzene@(**1a·2a**) were shifted downfield by 0.23 and 0.28 ppm for 1,4-diiodobenzene@(**1a·2a**) and by 0.05 and 0.10 ppm for 1,4-dibromobenzene@(**1a·2a**), respectively, relative to those of 1,4-dimethoxybenzene@(**1a·2a**), while the signals of the outer protons of the methylene-bridge rims of the **1a** and **2a** units in the guest@(**1a·2a**) were scarcely shifted (Figure 4a−c). This result indicates that the downfield shift of the inner protons is due to a CH−halogen interaction between the inner protons of the polarized methylene-bridge rims of the **1a** and **2a** units and the halogen atoms of the guest.[22] The size of the halogen atom affects the CH−halogen interaction,[22,24] and 1,4-diiodobenzene is the most suitable guest among 1,4-dihalobenzenes for interacting well with the inner protons of the methylene-bridge rims of **1a·2a**.

Item 4: CH−π interaction. The 1,4-dimethoxybenzene@(**1a·2a**) assemblage was formed by the addition of at least 2 equiv of 1,4-dimethoxybenzene to a 1:1 mixture of **1a** and **2a** (4.0 mM each) (Figure 4c). On the other hand, the addition of 30 equiv of *p*-ethyltoluene showed the moderate formation of *p*-ethyltoluene@(**1a·2a**) together with various aggregates (Figure 4h), although the size and shape of *p*-ethyltoluene are almost the same as those of 1,4-dimethoxybenzene.[24] In contrast, the addition of more than 30 equiv of *p*-xylene, 1,4-bis(trifluoromethyl)benzene, 1,4-diethylbenzene, or methoxybenzene to a 1:1 mixture of **1a** and **2a** did not induce the formation of guest@(**1a·2a**). This result indicates that CH−π interaction between the polarized methoxy protons of 1,4-dimethoxybenzene and the aromatic cavities of the **1a** and **2a** units is a driving force for the formation of 1,4-dimethoxybenzene@(**1a·2a**).[13,19,20]

Item 5: Orientation of encapsulated nonsymmetrical guest. It is noted that the orientation of a nonsymmetrical 1,4-disubstituted-benzene encapsulated in **1a·2a** can be strictly controlled.[15b] The following two results confirmed that the iodo and the methoxy groups of 1-iodo-4-methoxybenzene encapsulated in **1a·2a** are specifically oriented with respect to the cavities of the **2a** and **1a** units, respectively (Figures 4e and 5c). First, the fact that the upfield chemical shift change of the aromatic ortho proton with respect to the iodo group was larger than that with respect to the methoxy group ($\Delta\delta = -0.93$ vs -0.52) is consistent with the result discussed in item 2, in which the larger upfield shifted aromatic proton of the encapsulated guest was oriented toward the **2a** unit. Second, the signals of the inner protons of the methylene-bridge rims of the **2a** and **1a** units in 1-iodo-4-methoxybenzene@(**1a·2a**) were shifted downfield by 0.36 ppm and upfield by 0.04 ppm, respectively, relative to those in 1,4-dimethoxybenzene@(**1a·2a**). This result coincides with the result mentioned in item 3, in which the signals of the inner protons of the methylene-bridge rims of 1,4-diiodobenzene@(**1a·2a**) were shifted downfield relative to those of 1,4-dimethoxybenzene@(**1a·2a**) because of a CH−halogen interaction. This specific orientation of 1-iodo-4-methoxybenzene@(**1a·2a**) was also confirmed by X-ray crystallographic analysis (vide infra).

1-Ethyl-4-iodobenzene and 1-ethyl-4-methoxybenzene lack one of two interacting functional groups of 1-iodo-4-methoxybenzene. 1-Ethyl-4-iodobenzene and 1-ethyl-4-methoxybenzene also formed 1-ethyl-4-iodobenzene@(**1a·2a**) (Figure 4f) and 1-ethyl-4-methoxybenzene@(**1a·2a**) (Figure 4g), respectively, although more than 30 equiv of the guest were required in both cases. These results indicate the importance of multi-point interaction between the capsule and the guest. The chemical shifts of 1-ethyl-4-iodobenzene@(**1a·2a**) shown in Table 1 indicate that the iodo and the ethyl groups are specifically oriented with respect to the cavities of the **2a** and **1a** units, respectively (Figure 5d). The chemical shifts of 1-ethyl-4-methoxybenzene@(**1a·2a**) suggest that the methoxy and the ethyl groups are specif-

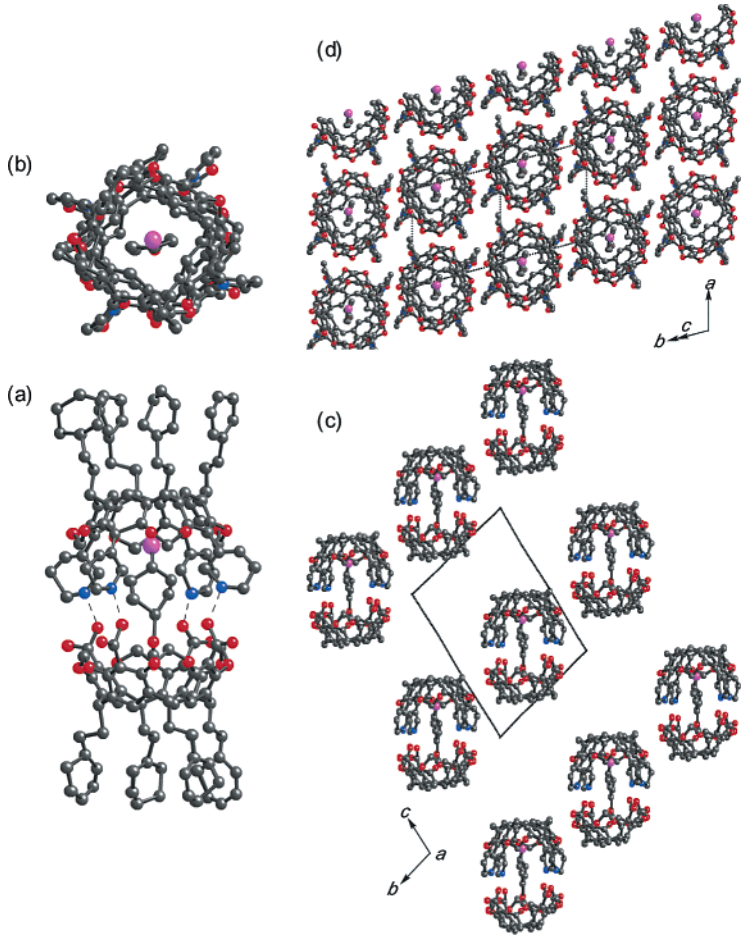

Figure 6. X-ray crystal structure of 1-iodo-4-methoxybenzene@(**1b·2b**): (a) front view and (b) top view. Packing diagram of 1-iodo-4-methoxybenzene@(**1b·2b**) in the crystal lattice: (c) front view and (d) top view, wherein the side chain (-CH_2CH_2Ph) of the heterodimeric capsule, two molecules of *p*-xylene and one molecule of water, which are not encapsulated, and hydrogen atoms are omitted for clarity.

ically oriented with respect to the cavities of the **2a** and **1a** units, respectively (Figure 5e). The orientation of *p*-ethyltoluene encapsulated in **1a·2a** was also specifically controlled (Figure 4h), although it is difficult to determine whether the methyl group is oriented to the cavity of **2a** or **1a** unit.

At this stage, it is not easy to elucidate the reason for the specific orientation of nonsymmetrical 1,4-disubstituted-benzene guests encapsulated in **1a·2a**, and we ought to wait for further studies such as calculation of electron density of the two-half cavities. At least it is conceivable that **2a** is a better host than **1a** for all interacting functional groups, from iodo downward because of its deeper cavity,[26] although **2a** alone did not interact with guests.

Item 6: Guest selectivity. In the competition experiment, guest-1@(**1a·2a**) and guest-2@(**1a·2a**) independently appeared on the NMR time scale (for example, Figure 4d). The ability of a guest to induce the formation of guest@(**1a·2a**) relatively increased in the order *p*-ethyltoluene < 1-ethyl-4-methoxybenzene ≤ 1-ethyl-4-iodobenzene ≤ 1,4-dibromobenzene < 1-iodo-4-methoxybenzene ≤ 1,4-dimethoxybenzene ≤ 1,4-diiodobenzene (Table 2).

Table 2. Guest Selectivity on Guest@(**1a·2a**) in the Competition Experiments[a]

guest-1@(**1a·2a**)	guest-2@(**1a·2a**)	selectivity[b]
p-I-Ph-I@(**1a·2a**)	*p*-MeO-Ph-OMe@(**1a·2a**)	1.17 ± 0.05:1
p-MeO-Ph-OMe@(**1a·2a**)	*p*-I-Ph-OMe@(**1a·2a**)	1.18 ± 0.05:1
p-MeO-Ph-OMe@(**1a·2a**)	*p*-Br-Ph-Br@(**1a·2a**)	26.8 ± 0.94:1
p-Br-Ph-Br@(**1a·2a**)	*p*-I-Ph-Et@(**1a·2a**)	1.23 ± 0.04:1
p-I-Ph-Et@(**1a·2a**)	*p*-MeO-Ph-Et@(**1a·2a**)	1.11 ± 0.01:1
p-MeO-Ph-Et@(**1a·2a**)	*p*-Me-Ph-Et@(**1a·2a**)	6.23 ± 0.12:1

[a] [**1a**] = [**2a**] = 4.0 mM in $CDCl_3$ at 23 °C in the presence of two kinds of guests (2 or 30 equiv of each). [b] Determined by the integration ratio of the signals of encapsulated guest-1 and guest-2.

Cold-Spray Ionization MS of Heterodimeric Capsule 1·2. Negative-mode cold-spray ionization (CSI) mass spectrometry was found to be a powerful method for the detection of guest@(**1a·2a**) in the presence of Ph_4PCl as a charge carrier.[18,27] As shown in Figure 3b, the negative-mode CSI-MS spectrum of a 1:1:1 mixture of **1a**, **2a**, and 1,4-diiodobenzene (4.0 mM each) in $CHCl_3$ in the presence of Ph_4PCl (1.3 mM), in which the ion source temperature is 0 °C, showed the molecular ion peak at *m*/*z* 2707.32 [1,4-diiodobenzene@(**1a·2a**) + Cl]$^-$ (calcd. 2708.05) in addition to the peak at *m*/*z* 2377.73 [**1a·2a** + Cl]$^-$ (calcd. 2378.21). Under the same conditions, the respective molecular ion peaks were observed at *m*/*z* 2516.6 [1,4-dimethoxybenzene@(**1a·2a**) + Cl]$^-$ (calcd. 2516.2) and at *m*/*z* 2611.3 [1-iodo-4-methoxybenzene@(**1a·2a**) + Cl]$^-$ (calcd. 2612.2) as shown in Figure 3c,d.

X-ray Crystal Structure of Heterodimeric Capsule 1·2. Single crystals of 1-iodo-4-methoxybenzene@(**1b·2b**) were obtained by slow evaporation of a solution of a 1:1 mixture of **1b** and **2b** (R = $(CH_2)_2$Ph) in a solvent mixture of $CHCl_3$ and *p*-xylene in the presence of 10 equiv of 1-iodo-4-methoxyben-

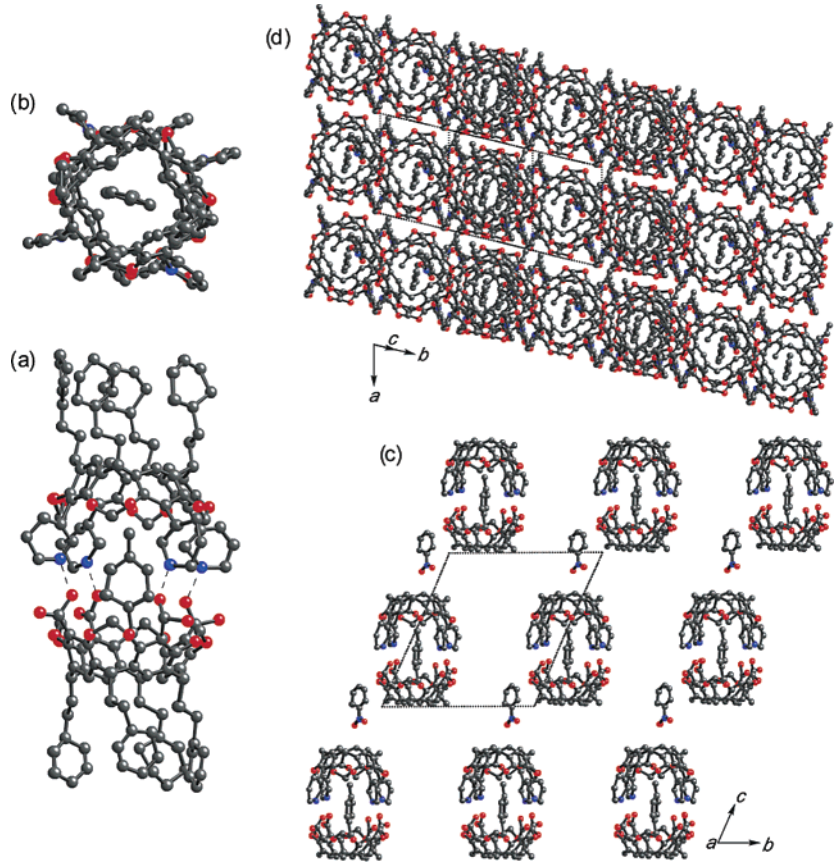

Figure 7. X-ray crystal structure of *p*-xylene@(**1b·2b**): (a) front view and (b) top view. Packing diagram of *p*-xylene@(**1b·2b**) and nitrobenzene in the crystal lattice: (c) front view and (d) top view, wherein the side chain (-CH_2CH_2Ph) of the heterodimeric capsule, five molecules of nonencapsulated *p*-xylene, and hydrogen atoms are omitted for clarity.

Table 3. Crystallographic Data for 1-Iodo-4-methoxybenzene@(**1b·2b**) and *p*-Xylene@(**1b·2b**)

	p-MeO-Ph-I@(**1b·2b**)/ 2*p*-xylene/H_2O	*p*-xylene@(**1b·2b**)/ 5*p*-xylene/$PhNO_2$
formula	$C_{175}H_{153}N_4O_{26}I$	$C_{206}H_{189}N_5O_{26}$
formula wt	2855.05	3150.78
crystal system	triclinic	triclinic
space group	*P*1	*P*1
a (Å)	12.408(2)	12.570(3)
b (Å)	15.433(3)	19.354(4)
c (Å)	21.717(4)	21.471(5)
α (deg)	101.477(3)	63.99(4)
β (deg)	104.861(4)	75.32(5)
γ (deg)	95.632(4)	76.08(5)
V (Å^3)	3890.1(11)	4490(2)
Z	1	1
temp (K)	183	103
R	0.164[a]	0.157[b]
R_w[c]	0.197	0.173

[a] $R = \sum|F_o - F_c|/\sum F_o$ for $I > 2\sigma(I)$. [b] $R = \sum|F_o - F_c|/\sum F_o$ for $I > 3\sigma(I)$. [c] $R_w = [\sum w(F_o - F_c)^2/\sum wF_o^2]^{1/2}$.

zene. Single crystals of *p*-xylene@(**1b·2b**) were grown by slow diffusion of *p*-xylene into a solution of a 1:1 mixture of **1b** and **2b** in nitrobenzene. The supramolecular structures of 1-iodo-4-methoxybenzene@(**1b·2b**) and *p*-xylene@(**1b·2b**) were determined by single-crystal X-ray diffraction analysis as shown in Figures 6 and 7, respectively.[28] Crystallographic data are summarized in Table 3.[28] The preliminary X-ray crystallographic analysis revealed that, in both cases, each molecule of **1b** and **2b** assembles into a heterodimeric capsule **1b·2b** in a rim-to-rim fashion through the four intermolecular $CO_2H\cdots N$ hydrogen bonds as shown in Figures 6a,b and 7a,b. Both the dihedral angles between the CO_2H groups and the resorcinol rings in the **1b** unit and between the 3-pyridyl groups and the resorcinol rings in the **2b** unit were apparently perpendicular. All of the N atoms of the four 3-pyridyl groups were directed inward to the cavity of the heterodimeric capsule, which is in agreement with the NOE data mentioned above. These orientations play essential roles in the formation of **1b·2b**. It is noted that one molecule of 1-iodo-4-methoxybenzene or *p*-xylene is exactly encapsulated in the cavity of **1b·2b** and that the guest encapsulated in **1b·2b** is oriented with the long axis of the guest along the long axis of **1b·2b** so as to maximize host−guest CH−halogen and/or guest−host CH−π interaction. The dimensions of 1-iodo-4-methoxybenzene@(**1b·2b**) were almost the same as those of *p*-xylene@(**1b·2b**) within the limits of preliminary crystal structures. The distances between the hydroxy oxygen atom of the carboxyl group and a diagonal one of **1b**, between the C2-hydrogen atom of the 3-pyridyl group and a diagonal one of **2b**, and between the bottom of the cavity of **1b** and that of **2b** are ca. 7.8, 6.6, and 13.1 Å, respectively. The preliminary X-ray crystallographic analysis of 1-iodo-4-methoxybenzene@(**1b·2b**) also confirmed that the iodo and the methoxy groups are specifically oriented with respect to the cavities of the **2b** and **1b** units, respectively, as discussed in the ^{1}H NMR study.

The packing diagrams of 1-iodo-4-methoxybenzene@(**1b·2b**) and *p*-xylene@(**1b·2b**) in the crystal lattice are shown in Figures 6c,d and 7c,d, respectively. It is noteworthy that the long axes of each of the heterodimeric capsules **1b·2b** are parallel and

that all of the **1b** and **2b** units are directed upward and downward, respectively. Thus, the dipole moments of each guest@(**1b·2b**) are aligned in parallel in the solid state.

Conclusion

We have demonstrated that each molecule of a tetracarboxylcavitand **1** and a tetra(3-pyridyl)-cavitand **2** assembles into a heterodimeric capsule **1·2** through four intermolecular $CO_2H\cdots N$ hydrogen bonds in a rim-to-rim fashion both in solution and in the solid state. In the ^1H NMR study, a 1:1 mixture of **1a** and **2a** (R = $(CH_2)_6CH_3$) in $CDCl_2CDCl_2$ or *p*-xylene-d_{10} exclusively produced the heterodimeric capsule **1a·2a** as a single species, whereas this mixture in $CDCl_3$ gave a mixture of various complicated aggregates. The addition of an appropriate 1,4-disubstituted-benzene as a guest template to a mixture of various complicated aggregates of the **1a** and **2a** in $CDCl_3$ shifted the thermodynamic equilibrium of the mixture toward guest@(**1a·2a**). As the electronic environment of the **1a** as a southern hemisphere is different from that of **2a** as a northern hemisphere, the inherently symmetrical guest becomes nonsymmetrical when encapsulated in **1a·2a**. The ability of a guest to induce the formation of guest@(**1a·2a**) in $CDCl_3$ increased in the order *p*-ethyltoluene < 1-ethyl-4-methoxybenzene ≤ 1-ethyl-4-iodobenzene ≤ 1,4-dibromobenzene < 1-iodo-4-methoxybenzene ≤ 1,4-dimethoxybenzene ≤ 1,4-diiodobenzene. The 1,4-disubstituted-benzene encapsulated in **1a·2a** was oriented with the long axis of the guest along the long axis of **1a·2a** so as to maximize CH−halogen interaction between the inner protons of the methylene-bridge rims (-O-$H_{out}CH_{in}$-O-) of the **1a** and **2a** units and the halogen atoms of 1,4-dihalobenzenes or CH−π interaction between the polarized methoxy protons of 1,4-dimethoxybenzene and the aromatic cavities of the **1a** and **2a** units. Therefore, the iodo and the methoxy groups of 1-iodo-4-methoxybenzene@(**1a·2a**) were specifically oriented with respect to the cavities of the **2a** and **1a** units, respectively. This result was also supported by the preliminary X-ray crystallographic analysis of 1-iodo-4-methoxybenzene@(**1b·2b**) (R = $(CH_2)_2Ph$). Thus, the CH−halogen and/or CH−π interaction between the heterodimeric capsule and a guest, as well as the size and shape of a guest with respect to the cavity of the capsule, are important cooperative factors for inducing the formation of a thermodynamically stable guest@(**1·2**) with the complementary $CO_2H\cdots N$ hydrogen bonds between **1** and **2** and to strictly control the orientation of the encapsulated nonsymmetrical guest. In the crystal lattice, the dipole moments of each guest@(**1b·2b**), where the guest is 1-iodo-4-methoxybenzene or *p*-xylene, were aligned in parallel. Control of the orientation of an encapsulated guest in solution, as well as that of a guest-encapsulating heterodimeric capsule in the solid state, would endow the guest@(**1·2**) with potential as a building block for molecular devices.[9c,d] Studies are in progress into the exploration of appropriate guests, which can be encapsulated in the heterodimeric capsule **1·2**, with functions directed toward supramolecular gyroscope[29] and nonlinear optics.[30]

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Supporting Information Available: X-ray experimental details in the form of a crystallographic information file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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